Efficient Conversion of Cephalomannine to Paclitaxel and 3′-*N*-Acyl-3′-*N*-debenzoylpaclitaxel Analogs

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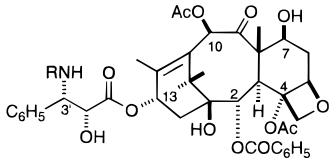
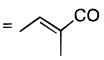
Received January 13, 1997

The clinically important anticancer drug paclitaxel (Taxol) (**1**)[1] was, until recently, available only by a complex and expensive isolation process from *Taxus brevifolia* bark, which is a nonrenewable and relatively scarce resource. This dependence on bark as the source of a drug required in ever increasing amounts focused both public and scientific interest on the discovery of alternate sources,[2] and several approaches to the production of paclitaxel have been investigated. Total synthesis is the most fundamental approach to this problem, and to date four total syntheses of paclitaxel have been reported,[3] but regrettably none of these syntheses is as yet suitable for large-scale production. Other approaches have included plant tissue culture and fungal culture,[4] but the major current commercial production method is that of partial synthesis from 10-deacetylbaccatin III,[5] which is available in reasonable yield from the needles of *Taxus baccata* and other *Taxus* species.[6]

Although the partial synthesis of paclitaxel from 10-deacetylbaccatin III has alleviated the immediate paclitaxel supply problem, paclitaxel is still being obtained by direct isolation from *T. brevifolia* bark and the needles of various *Taxus* species.[7] This process yields not only paclitaxel (**1**) but also the closely related compound cephalomannine (**2**), which differs from paclitaxel only in that it has an *N*-tigloyl group rather than an *N*-benzoyl group on the side chain.[8] Cephalomannine is difficult to



1 R = C_6H_5CO

2 R = 

separate from paclitaxel, but it does represent a potentially valuable additional source of this compound, especially since it can occur in *Taxus* species in amounts that exceed those of paclitaxel.[9] One possible approach to the required conversion of cephalomannine to paclitaxel is by the known chemistry of separation from paclitaxel followed by cleavage of the side chain to produce baccatin III,[10] followed by protection at C-7, acylation at C-13 with the paclitaxel side chain, and deprotection.[5] This procedure is a lengthy one, and we thus sought an alternate approach that would provide the desired conversion more efficiently. Ideally this conversion would be effective either on purified cephalomannine or on a mixture of paclitaxel and cephalomannine, thus avoiding the difficult separation of the two compounds. We now report the efficient achievement of such a conversion.

Conceptually, the direct conversion of cephalomannine (**2**) to paclitaxel (**1**) involves a transamidation reaction, or selective removal of the *N*-tigloyl group followed by N-benzoylation. The presence of various reactive groups in cephalomannine such as its ester and oxetane functions precluded the use of vigorous conditions for the removal of the *N*-tigloyl group and even prevented the use of reagents which are selective for amide cleavage. Thus Meerwein's reagent, which normally will form imino ethers from amides in the presence of esters,[11] gave only oxetane ring-opened products with paclitaxel[12] and would presumably give the same type of reaction with cephalomannine. Similarly, selective hydrolysis of 2′-*O*,7-*O*,3′-*N*-tris(*tert*-butoxycarbonyl)paclitaxel gave no N-debenzoyl product, yielding instead the 2-debenzoyl analog and thus opening up a route to the synthesis of such analogs.[13] This reaction on cephalomannine would also presumably give the same 2-*O*-debenzoyl product rather

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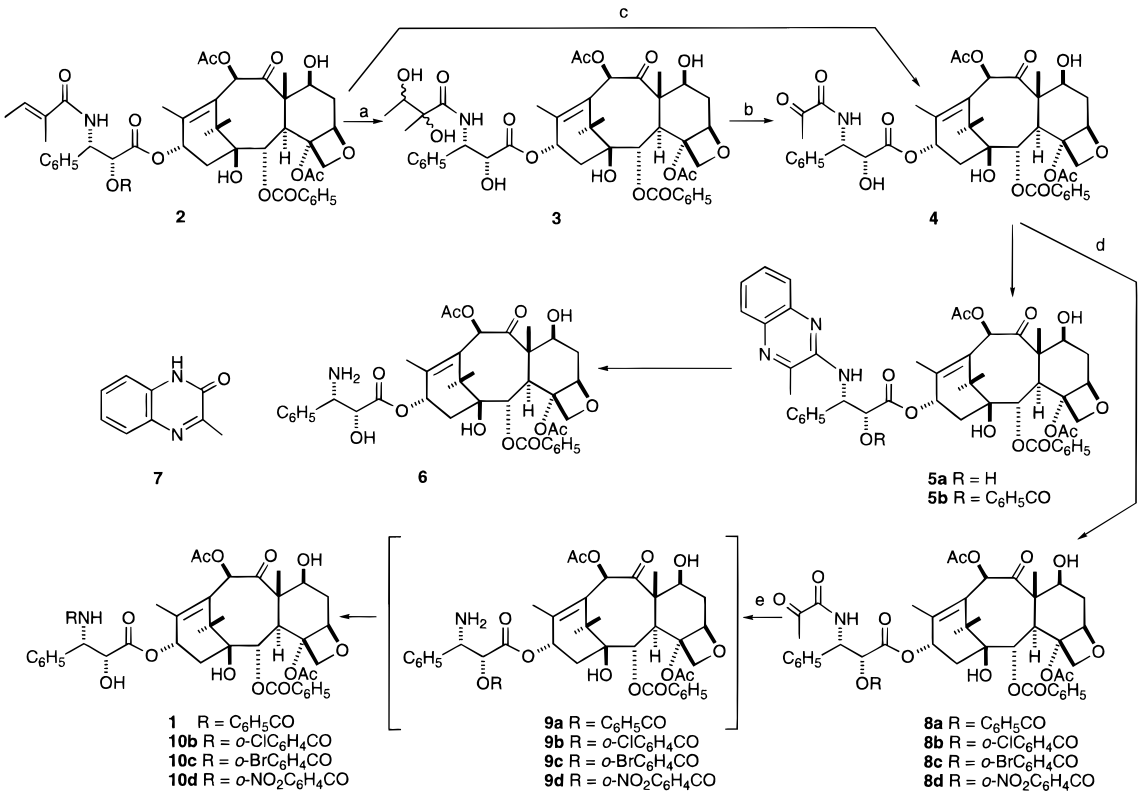
S0022-3263(97)00063-7 CCC: $14.00

Scheme 1[a]



[a] Key: (a) OsO_4 (catalytic), *t*-BuOOH, Et4NOAc, acetone, 0 °C, 1 h; (b) $NaIO_4$, H_2O, rt 1 h; (c) O_3, CH_2Cl_2, −78 °C, 30 min, then −78 °C, 15 min; (d) ArCOOH, DCC, 4-PP, EtOAc, rt, 2−4 h; (e) *o*-phenylenediamine, *p*-TsOH, dry C_6H_6, reflux, 12−18 h.

than the 3′-*N*-detigloyl derivative. Devising a selective and direct conversion of cephalomannine to paclitaxel was thus not a trivial undertaking.

As noted above, paclitaxel and cephalomannine have similar chromatographic properties and are difficult to separate from each other. In earlier work, we devised a practical method for the separation of paclitaxel from cephalomannine which took advantage of the fact that the 11,12-double bond of both compounds is very unreactive[14] while the double bond of the tigloyl group has a normal reactivity. Selective osmylation of the side chain of cephalomannine to give the diol mixture **3** can thus readily be achieved, and diols **3** can be easily separated from paclitaxel by flash chromatography.[15] The availability of the diol mixture **3** prompted us to investigate its conversion to paclitaxel.

Our synthetic strategy was based on the observation that oxidation of the diol mixture **3** or direct ozonolysis of cephalomannine[16] readily yields the ketoamide **4**. It seemed reasonable to assume that **4** would react readily with *o*-phenylenediamine to give the 2-aminoquinoxaline **5a** and that this would then undergo acid hydrolysis to give the amino alcohol **6** and the quinoxalinone **7**. The facile hydrolysis of 2-aminoquinoxalines has been known for over 100 years; as an example, hydrolysis of 2,3-diaminoquinoxaline with hydrochloric acid gives 3-amino-2-quinoxalinone under relatively mild conditions.[17] In the event, the diastereomeric mixture of cephalomanninediols (**3**) could be oxidized to the ketoamide **4** in 93% yield by treatment with sodium periodate in methanol. In an alternative approach, the ketoamide **4** could be obtained directly from cephalomannine in 97% yield by ozonolysis. Treatment of the ketoamide **4** with *o*-phenylenediamine and a catalytic quantity of *p*-toluenesulfonic acid in refluxing benzene did not yield the quinoxaline **5** but instead gave the free amine **6**, albeit in low yield. The low yield was most probably due to difficulties in workup of the basic product, and so a strategy was devised to circumvent this difficulty. The ketoamide **4** was first converted to its 2′-*O*-benzoyl derivative **8a** in 92% yield by selective acylation with benzoic acid under standard DCC/DMAP conditions. The 2′-*O*-benzoate **8a** was then treated with *o*-phenylenediamine and *p*-toluenesulfonic acid in refluxing benzene to achieve a direct transformation to paclitaxel (**1**) in one pot; the yield proved to be a very satisfactory 91%. The conversion presumably proceeds through the free quinoxaline **5b** and thence to the *O*-benzoylamino alcohol **9a**, which then undergoes intramolecular O → N transacylation to give **1**.

*This sequence of steps thus provides a simple and high-yield process for the conversion of cephalomannine (**2**) to paclitaxel (**1**).* If the ozonolysis route is selected, the overall yield is 81%. The route *via* the diol **3** has a lower overall yield of 73% assuming a yield of 94% for the conversion of cephalomannine to its diol,[15] but it has the advantage of simultaneously providing a simple method for the separation of paclitaxel from cephalomannine.

Having achieved the goal of a simple conversion of cephalomannine to paclitaxel, we next investigated the generality of the reaction by using it to prepare three paclitaxel analogs in which the 3′-*N*-benzoyl group was

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Table 1. Biological Evaluation of 10b−d

no.	compd name	cytotoxicity to P-388 murine leukemia[a]	
		ED_{50}	ED_{50}/ED_{50}(paclitaxel)
1	paclitaxel	0.0029	1.0
10b	*N*-debenzoyl-*N*-(*o*-chlorobenzoyl)paclitaxel	0.013	4.5
10c	*N*-debenzoyl-*N*-(*o*-bromobenzoyl)paclitaxel	0.074	25.0
10d	*N*-debenzoyl-*N*-(*o*-nitrobenzoyl)paclitaxel	0.13	45.0

[a] ED_{50} refers to the concentration which produces 50% inhibition of proliferation after 48 h incubation.

replaced with an *o*-substituted benzoyl group. The three analogs **10b**−**d** were prepared by the procedure described above but substituting *o*-chloro-, *o*-bromo-, or *o*-nitrobenzoic acid for the benzoic acid of the original process to give the 2′-*O*-aroyl derivatives **8b**−**d**. Treatment of **8b**−**d** with *o*-phenylenediamine as described above gave the paclitaxel analogs **10b**−**d** in good yield.

The cytotoxicities of the 3′-*N*-aroyl analogs **10b**−**d** were determined in the P-388 murine lymphocytic leukemia system; the results are shown in Table 1.[18] All three analogs were less cytotoxic than paclitaxel in this bioassay, suggesting that an *ortho* substitution on the 3′-*N*-benzoyl group is deleterious to the cytotoxicity of paclitaxel.

Experimental Section

General Methods. All chemicals were procured from Aldrich Chemical Co. and used without further purification. All anhydrous reactions were performed in oven-dried glassware under a positive pressure of argon. Solvents used in anhydrous reactions were freshly distilled over appropriate dehydrating agents. All reactions were monitored by TLC (silica gel, GF), analyzed with UV light, and developed with vanillin/H_2SO_4 spray. ^{1}H NMR spectra were obtained at 270 or 400 MHz, and ^{13}C NMR spectra were obtained at 100.57 MHz. All NMR spectra were recorded in $CDCl_3$ using solvent (δ_C 77.0 ppm) or residual $CHCl_3$ (δ_H 7.24 ppm) as internal standards. Coupling constants are reported in hertz (Hz). ^{1}H and ^{13}C NMR spectra were assigned primarily by comparison of chemical shifts and coupling constants with those of related compounds. Some ^{1}H NMR spectra showed the presence of traces of ethyl acetate; paclitaxel and its derivative retain ethyl acetate very tightly, and it cannot be removed completely even on prolonged treatment in vacuo at 38 °C. Exact mass measurements were performed at the Nebraska Center for Mass Spectrometry.

Dihydroxylation of Cephalomannine (2) in a Mixture of Paclitaxel (1) and 2. A crude mixture (1.0 g, *ca*. 80% pure; ratio of **1:2**, *ca*. 80:20 by ^{1}H NMR) of **1** and **2** in acetone (10 mL; HPLC grade) was treated with $Et_4NOAc{\cdot}4H_2O$ (80 mg), ^{t}BuOOH (70% in H_2O, 300 μL), and OsO_4 (2.5% in ^{t}BuOH, 300 μL, catalytic) at 0 °C. Purification of the crude product (900 mg) as described previously[15] afforded pure paclitaxel (**1a**) (570 mg) and a diastereomeric mixture of cephalomanninediols **3** (150 mg), having spectral properties identical with those previously reported.[15]

Oxidation of Cephalomanninediols 3 to the Ketoamide 4. To a solution of cephalomanninediols (**3**) (140 mg, 0.16 mmol) in a mixture of MeOH (4.0 mL) and water (1.0 mL) was added $NaIO_4$ (55 mg, 0.25 mmol). The reaction mixture was stirred at 25 °C for 3 h, after which MeOH was evaporated and the product extracted with EtOAc. The organic layer was washed successively with water and brine and dried over Na_2SO_4. Concentration under reduced pressure gave pure ketoamide **4** (120 mg, 93%) as an amorphous solid which resisted crystallization. Compound **4**: ^{1}H NMR ($CDCl_3$) δ 1.15 (s, 3H), 1.24 (s, 3H), 1.67 (s, 3H), 1.80 (s, 3H), 1.80−1.90 (m, 1H), 2.20−2.40 (m, 1H), 2.24 (s, 3H), 2.34 (s, 3H), 2.38 (s, 3H), 2.44−2.60 (m, 2H), 3.50 (br s, 1H), (m, 2H, 6-H), 3.79 (d, J = 6.9, 1H), 4.18 (d, J = 8.5, 1H), 4.30 (d, J = 8.5, 1H), 4.37 (m, 1H), 4.66 (d, J = 2.8, 1H), 4.94 (d, J = 7.6, 1H), 5.48 (dd, J = 2.8, 9.3, 1H), 5.66 (d, J = 6.9, 1H), 6.18 (t, J = 7.0, 1H), 6.27 (s, 1H), 7.28−7.65 (m, 8H), 7.80 (d, J = 9.3, 1H), 8.12 (d, J = 7.0, 2H); ^{13}C NMR δ 9.53, 14.83, 20.81, 21.65, 22.54, 24.48, 26.80, 35.48, 35.59, 43.14, 45.65, 54.93, 58.48, 72.07, 73.30, 74.83, 75.49, 76.42, 76.68, 78.98, 81.14, 84.31, 126.98, 128.60, 128.89, 128.94, 129.43, 130.12, 133.18, 133.74, 137.08, 141.73, 159.62, 166.92, 170.35, 171.16, 171.92, 196.30, 203.47; HRFABMS calcd for $C_{43}H_{50}NO_{15}$ [M + H]$^+$ m/z 820.3102, found 820.3137.

Ozonolysis of Cephalomannine (2) to the Ketoamide 4. A solution of cephalomannine (166.2 mg, 2.0 mmol) in dry CH_2Cl_2 (15 mL) was cooled to −78 °C, and ozone was passed through the solution for 30 min during which the color of the solution changed from colorless to pinkish blue. The solution was allowed to stir at −78 °C for an additional 15 min, after which nitrogen was purged through the solution for 10 min. Evaporation under reduced pressure afforded a crude material. Purification by column chromatography over silica gel (hexane:EtOAc, 1:1) afforded **4** (158.0 mg, 97%) identical with the sample obtained above.

General Procedure for the Preparation of 2′-*O*-Aroyl Derivatives 8a−d. The aromatic carboxylic acid (0.043 mmol, 1.2 equiv), dicyclohexylcarbodiimide (11.1 mg, 0.054 mmol), and pyrrolidinopyridine (2.0 mg; catalytic) were dissolved in dry EtOAc (2 mL) and stirred at room temperature for 10 min. To this mixture was added **4** (30.0 mg, 0.036 mmol), and the mixture was stirred at room temperature for 2−4 h (TLC control). The mixture was then filtered through a bed of silica gel and Celite. Evaporation of the filtrate under reduced pressure afforded the crude product which on purification by preparative TLC (silica gel; hexane:EtOAc, 1:1) yielded the corresponding 2′-*O*-aroyl derivatives **8a**−**d** as amorphous solids in 79−91% yields.

Compound 8a: ^{1}H NMR δ 1.14 (s, 3H), 1.25 (s, 3H), 1.64 (s, 3H), 1.85 (s, 3H), 1.95−2.05 (m, 1H), 2.18−2.24 (m, 1H), 2.20, 2.35, and 2.38 (s, 3H each), 2.46−2.58 (m, 2H), 3.78 (d, J = 6.8, 1H), 4.15 (d, J = 8.6, 1H), 4.25 (d, J = 8.6, 1H), 4.44 (m, 1H), 4.95 (br d, J = 7.5, 1H), 5.55 (d, J = 3.4, 1H), 5.64 (d, J = 6.8, 1H), 5.70 (dd, J = 3.4, 8.8, 1H), 6.20 (t, J = 7.0, 1H), 6.23 (s, 1H), 7.25−7.62 (m, 11H), 7.80 (d, J = 8.8, 1H), 8.00, 8.10 (d, J = 7.0, 2H each); ^{13}C NMR δ 9.59, 14.81, 20.80, 22.16, 22.54, 24.41, 26.80, 35.35, 35.43, 43.14, 45.52, 53.30, 58.42, 71.99, 72.05, 74.56, 75.11, 76.35, 79.35, 80.98, 84.43, 126.73, 128.32, 128.66, 128.72, 128.97, 129.18, 129.21, 129.90, 130.16, 132.69, 133.72, 134.00, 135.88, 142.76, 159.53, 165.44, 167.03, 167.78, 169.63, 171.25, 196.12, 203.75; HRFABMS calcd for $C_{50}H_{54}NO_{16}$ [M + H]$^+$ m/z 924.3364, found 924.3391.

Compound 8b: ^{1}H NMR δ 1.14 (s, 3H), 1.25 (s, 3H), 1.67 (s, 3H), 1.8−2.4 (m, 3H), 1.94 (s, 3H), 2.22 (s, 3H), 2.32 (m, 1H), 2.38 (s, 3H), 2.39 (s, 3H), 2.4−2.6 (m, 2H), 3.81 (d, J = 6.8, 1H), 4.19 (d, J = 8.6, 1H), 4.30 (d, J = 8.6, 1H), 4.45 (m, 1H), 4.97 (br d, J = 7.4, 1H), 5.64 (d, J = 3.4, 1H), 5.70 (d, J = 6.8, 1H), 5.75 (dd, J = 2.9, 8.8, 1H), 6.29 (s, 1H), 6.29 (t, 1H), 7.30−7.90 (m, 13H), 8.13 (d, J = 7.0, 2H).

Compound 8c: ^{1}H NMR δ 1.14 (s, 3H), 1.26 (s, 3H), 1.67 (s, 3H), 1.95 (s, 3H), 2.0−2.4 (m, 3H), 2.22 (s, 3H), 2.32 (m, 1H), 2.39 (s, 3H), 2.41 (s, 3H), 2.50 (d, J = 2.0, 1H), 2.50−2.65 (m, 1H), 3.81 (d, J = 6.8, 1H), 4.19 (d, J = 8.6, 1H), 4.30 (d, J = 8.6, 1H), 4.45 (m, 1H), 4.97 (br d, J = 7.4, 1H), 5.64 (d, J = 3.4), 5.70 (d, 1H, J = 6.8), 5.75 (dd, J = 2.9, 8.8, 1H), 6.29 (s, 1H), 6.29 (t, J = 7.0, 1H), 7.30−7.80 (m, 13H), 8.13 (d, J = 7.0, 2H).

Compound 8d: ^{1}H NMR δ 1.13 (s, 3H), 1.24 (s, 3H), 1.66 (s, 3H), 1.8−2.0 (m, 1H), 1.93 (s, 3H), 2.1−2.4 (m, 2H), 2.22 (s, 3H), 2.32 (m, 1H), 2.39 (s, 3H), 2.4−2.6 (m, 1H), 2.40 (s, 3H), 2.50 (d, J = 2.0, 1H), 2.53 (m, 2H), 3.80 (d, J = 6.8, 1H), 4.17 (d, J = 8.2, 1H), 4.31 (d, J = 8.2, 1H), 4.44 (m, 1H), 4.97 (br d, J = 7.9,

(18) Cytotoxicities were determined by Dr. W. Lichter, University of Miami, using established NCI protocols.

1H), 5.63 (m, 3H), 6.20 (t, J = 7.0, 1H), 6.28 (s, 1H), 7.32−7.98 (m, 13H), 8.13 (d, J = 7.3, 2H).

General Procedure for the Preparation of 3′-*N*-Aroyl Derivatives 1 and 10b−d. To a solution of 2′-*O*-aroyl compound **8a**−**d** (0.025 mmol) in dry benzene (5 mL) were added activated molecular sieves (4 Å, 3 balls), *o*-phenylenediamine (27.0 mg, 0.25 mmol), and *p*-toluenesulfonic acid (2.0 mg; catalytic). The mixture was then refluxed on an oil bath for 12−18 h (TLC control). The color changed from yellow orange to dark red. The mixture was allowed to cool to room temperature, diluted with EtOAc (10 mL), and washed successively with dilute HCl (1 N) followed by water and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude products obtained were purified by preparative TLC (silica gel; hexane:EtOAc, 1:1) to yield the corresponding 3′-*N*-aroyl analogs **10b**−**d**, as amorphous solids in 70−91% yields.

Paclitaxel (1). Paclitaxel was obtained from **8a** in 91% yield. Spectral data (^{1}H and ^{13}C NMR and LRFABMS) were identical with those reported for paclitaxel.[13]

Compound 10b: ^{1}H NMR δ 1.14 (s, 3H), 1.25 (s, 3H), 1.67 (s, 3H), 1.8−1.9 (m, 1H), 1.82 (s, 3H), 2.23 (s, 3H), 2.35−2.4 (m, 1H), 2.38 (s, 3H), 2.48 (br s, 1H), 2.5−2.65 (m, 1H), 3.50 (br s, 1H), 3.80 (d, J = 7.0, 1H), 4.19 (d, J = 8.0, 1H), 4.29 (d, J = 8.0, 1H), 4.44 (m, 1H), 4.76 (br s, 1H), 4.95 (d, J = 7.8, 1H), 5.67 (d, J = 7.0, 1H), 5.80 (br d, J = 9.0, 1H), 6.23 (t, J = 7.0, 1H), 6.28 (s, 1H), 7.10 (d, J = 9.0, 1H), 7.24−7.60 (m, 12H), 8.11 (d, J = 8.5, 2H); HRFABMS m/z [M + H]$^+$ calcd for $C_{47}H_{51}O_{14}NCl$ 888.2998, found 888.2976.

Compound 10c: ^{1}H NMR δ 1.14 (s, 3H), 1.26 (s, 3H), 1.68 (s, 3H), 1.8−1.9 (1H, m), 1.83 (s, 3H), 2.2−2.4 (m, 1H), 2.24 (s, 3H), 2.37 (s, 3H), 2.47 (br s, 1H), 2.47−2.6 (m, 2H), 3.48 (br s, 1H), 3.80 (d, J = 7.0, 1H), 4.19 (d, J = 8.0, 1H), 4.29 (d, J = 8.0, 1H), 4.45 (m, 1H), 4.77 (br d, J = 1.2, 1H), 4.95 (d, J = 7.8, 1H), 5.68 (d, J = 7.0, 1H), 5.79 (dd, J = 1.2, 9.0, 1H), 6.28 (m, 1H), 6.28 (s, 1H), 6.84 (d, J = 9.0, 1H), 7.24−7.60 (m, 12H), 8.10 (d, J = 8.5, 2H); FABMS m/z [M + H]$^+$ calcd for $C_{47}H_{50}O_{14}NBr$ [M + H]$^+$ 934 and 932, found 934 and 932.

Compound 10d: ^{1}H NMR δ 1.15 (s, 3H), 1.30 (s, 3H), 1.68 (s, 3H), 1.8−1.9 (m, 1H), 1.85 (s, 3H), 2.24 (s, 3H), 2.3−2.4 (m, 1H), 2.36 (s, 3H), 2.4−2.6 (m, 2H), 2.45 (br s, 1H), 2.50 (m, 2H), 3.48 (br s, 1H), 3.80 (d, J = 7.0, 1H), 4.21 (d, J = 8.0, 1H), 4.28 (d, J = 8.0, 1H), 4.46 (m, 1H), 4.83 (br s, 1H), 4.95 (d, J = 7.8, 1H), 5.68 (d, J = 7.0, 1H), 5.82 (br d, J = 9.0, 1H), 6.29 (s, 1H), 6.42 (t, J = 7.0, 1H), 6.71 (d, J = 9.0, 1H), 7.40−7.65 (m, 11H), 8.01 (d, J = 8.0, 1H), 8.08 (d, J = 8.5, 2H, *o*-H of 2-benzoyl); HRFABMS m/z [M + H]$^+$ calcd for $C_{47}H_{51}O_{16}N_2$ 899.3238, found 899.3212.

Acknowledgment. This work was supported by a grant from the National Cancer Institute, Grant No. RO1 CA55131, and this support is gratefully acknowledged. A gift of crude paclitaxel-containing fractions from *T. brevifolia* by Dr. K. Snader, NCI, is also gratefully acknowledged.

Supporting Information Available: Copies of ^{1}H NMR spectra and a listing of NMR peak assignments of compounds **4**, **8a**−**d**, and **10b**−**d** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9700639